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Effects of chronically high levels of aldosterone on different cognitive dimensions – an investigation in patients with primary aldosteronism

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Abstract:

Primary aldosteronism is a natural model for chronic aldosterone excess in humans and associated with symptoms of anxiety and depression. Cognitive deficits are inherent to the symptomatology of depression and anxiety disorders. Mineralocorticoid receptors and aldosterone appear to play a role in memory. Aldosterone was additionally supposed to be a risk factor for cognitive decline in patients with essential hypertension. The objective of this study was to investigate possible effects of chronically high aldosterone concentrations on cognitive function. A range of cognitive dimensions were assessed in 19 patients (9 males, 10 females; mean age 47.1 (12.5) under standardized treatment and several rating scales for anxiety, depression, quality of life and sleep were administered. Cognitive parameters were compared to standard norms from a large, healthy standardization sample. Patients showed increased levels of anxiety and depression without meeting diagnostic criteria for a disorder. Besides a numerically lower attention score, patients did not show any significant differences in the cognitive dimensions. Anxiety and depression were negatively correlated with quantitative performance in males. In females, a negative correlation between sleep disturbances and abstract reasoning and a positive correlation with quantitative performance were found. Our data showed no specific effect of chronic aldosterone in the tested cognitive parameters overall at least in younger patients, but they indicate sexually dimorphic regulation processes.

Keywords: primary aldosteronism, anxiety, depression, cognition, mineralocorticoidreceptor

1. Introduction

Patients with primary aldosteronism (PA) are thought to be a natural model for chronic aldosterone excess, showing significantly higher scores for depression and anxiety compared to the general population, with females being more affected than males ¹. These patients were also found to have a lower quality of life (QoL) even after treatment with either a mineralocorticoid receptor (MR) antagonist or adrenalectomy (ADX) ². Cognitive deficits are prevalent in depression ^{3,4}; however, the underlying pathophysiology is not fully clarified. Animal data emphasizes the importance of a balanced mineralocorticoid receptor (MR)/glucocorticoid receptor (GR) system for cognitive functions ⁵ and support the role of MR in memory functions. Furthermore the MR seems to be involved in emotional memory processes ⁶⁻⁸. Both the MR and aldosterone appear to be involved in the pathophysiology of depression and anxiety ^{9,10}. Subchronic treatment with aldosterone resulted in increased anxiety and depression-like behaviour in rats. Furthermore changes in the transcription of hippocampal genes, which are involved in synaptic and neuronal remodelling were found ^{11,12}. Similar results were reported for depression-like behaviour in rats after chronic treatment with a MR agonist ¹³. In humans, the MR has been shown to predict memory performance in depression (Keller et al., 2017) and blocking the MR in animals resulted in an impairment of the reference memory ¹⁴. After administration of the MR-antagonist spironolactone in healthy male controls, impaired cognitive performance in selective attention, delayed recall, and set shifting/mental flexibility was observed ¹⁵. In patients with depression, elevated aldosterone concentrations were described ^{16,17}, and polymorphisms in the angiotensin converting enzyme (ACE)-gene were reported to be associated with unipolar depression and hypercortisolism ¹⁸. Again hypertension itself has been found to be related to cognitive impairment and the development of dementia ¹⁹. Yagi et al. could additionally identify high plasma aldosterone as a risk factor for cognitive decline in patients with essential hypertension ²⁰. Similar results were found in elder patients with essential hypertension. In these patients aldosterone was associated with lower blood flow and patients with higher concentrations of aldosterone were found to improve in cognitive functions when treating blood pressure ²¹.

The aim of the present study was to specify the effects of aldosterone on cognitive functions and gain insight into possible pathways of cognition mediated by MR and aldosterone.

2. Methods

Patients

19 patients (9 males, 10 females; mean age 47.1 ± 12.5 years; age range 18-66 years) with first diagnosed PA were enrolled in this study. Patients were prospectively recruited from the German Conn Registry. All patients had to give their written informed consent and were investigated under standardized antihypertensive medication according to the conn-registry-protocol (a combination of Verapamil, Doxazosin, and/or Urapidil), not affecting the renin-aldosterone-angiotensine-system (RAAS) ²². The diagnosis of PA was based on established criteria ^{23,25}. A full examination with regard to basic clinical and laboratory data and several psychiatric and neuropsychological scales was performed.

Patients doing shift work or suffering from jetlag, or being treated with spironolactone, any psychiatric drugs, or hormonal therapy were excluded. Use of drugs or extensive abuse of alcohol was not allowed. Patients with further hormonal disturbances or known sleeping disorders were not enclosed.

The study was performed in accordance with the Declaration of Helsinki and with the "Note for Guidance on Good Clinical Practice for Studies on Medical Products in the European Community, July 11, 1990". The study was approved by the ethical committee of the University of Munich.

Investigations and psychiatric assessments were performed by physicians and medically trained staff. The neuropsychological and psychological testing was performed by professionally trained staff at the Max-Planck-Institute of Psychiatry.

Psychiatric scales

Quality of life was assessed with the SF-12 questionnaire, a validated, multipurpose measure, which can discriminate between mental and physical aspects of quality of life ²⁶. Reference values were set by the norm sample of the German population (1994) (SF-12 Manual).

To assess depression and anxiety, we performed the Beck Inventory of Depression (BDI), the Patient Health Questionnaire-9 (PHQ-9), the Hamilton Rating Scale for Depression (HAM-D), the generalized anxiety disorder questionnaire (GAD-7), and the Hamilton Anxiety Rating Scale (HAM-A).

The BDI, the HAM-D, and the PHQ-9 are validated measuring scales widely used for screening, diagnosing and specifying the severity of depression ²⁷⁻²⁹. The HAM-A and GAD-7 are instruments to identify and quantify the extent of anxiety ^{29, 30}.

Reference data for the BDI was provided by Beck et al. ²⁸. Scores of 1-10 indicate no depression, scores from 10-19, 20-29, and ≥ 30 indicate a mild, moderate, or severe depressive syndrome, respectively ^{31, 32}.

Concerning the HAM-D, reference data was provided by Zimmerman et al. ³³. A score of ≤ 8 indicates no depression, a mild depressive syndrome was defined for the range of 9-16 points, a moderate syndrome for 17-24 points, and a severe syndrome for ≥ 25 points ³².

Reference data for the PHQ-9 was taken by Rief et al. ³⁴. Scores of 5, 10, 15, and 20 represented cut-points for mild, moderate, moderately severe and severe depression, respectively ³⁵.

Concerning the GAD-7, normative data of the German population was defined by Lowe et al. ³⁶. According to the cut-offs set by Spitzer et al. ³⁰, scores of 5, 10, and 15 represent cut-off points for mild, moderate and severe anxiety.

We used the HAM-A grading of severity suggested by Hamilton et al. ³⁷. Ranges of 14-17, 18-24, and 25-30 points indicate a mild, moderate, or moderate to severe level of anxiety.

Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI). The PSQI is able to evaluate retrospectively the quality and patterns of sleep over a time interval of one month by observing seven different components which can be combined in a global score ³⁸. Additionally we performed three sum scores to gain further insight to sleep quality:

(1) "Sleep Efficiency Sum Score" composed of "Sleep Duration" and "Sleep Efficiency"; (2) "Perceived Sleep Quality Sum Score" composed of "Subjective Sleep Quality", "Sleep Latency", and "Use of Sleeping Medication"; (3) "Daily Disturbances Sum Score" composed of "Sleep Disturbances" and "Daytime Dysfunction".

PSQI reference values from the Austrian population were used ³⁹.

Daily fatigue was assessed with the Epworth Sleepiness Scale (ESS) ⁴⁰ using German normative values ⁴¹.

Neuropsychological assessment

Neuropsychological testing was performed in the morning. Cognitive performance was evaluated using the d2 test for attention (d2), a validated test to rate selective attention and concentration ⁴². Test parameters for quantitative performance were total number of items processed ("GZ") and total number of items minus errors, i.e., number of correctly marked items ("GZ-F"). Qualitative performance was represented by the percentage of errors ("F%").

Logical memory was evaluated with the Revised Wechsler Memory Scale ⁴³, which examines immediate ("Logical Memory I") and delayed ("Logical Memory II" after 30 minutes) text reproduction. Executive abilities were assessed with two subtests of the Wechsler Test of Intelligence (WIE). "Matrices" measures abstract reasoning and fluid intelligence. The "Digit-Symbol-Test" (DST) assesses processing speed ⁴⁴. To observe gender-dependent differences, raw data of the different scales were compared. Patients' cognitive parameters were compared to norm values of the general population.

Hormone assays

Blood draw for the laboratory routine and hormones cortisol and aldosterone was performed in a standardized procedure in the morning after resting for 10 min. Plasma aldosterone concentrations were measured using a commercial radioimmunoassay (DiaSorin Liasion CLIA Aldosteron ng/l). Plasma renin concentrations were determined using a chemiluminescence immunoassay (ReninLiasion Diasorin Liaison Act. 4.4-64uU/ml, Italy). Cortisol was measured with a chemiluminescence immunoassay (Liaison Diasorin REF 313261).

Statistical analysis

Statistical analyses were carried out in SPSS Statistics for Windows, version 23 (IBM). Analysis of variance with age as a covariate (ANCOVA) was performed to examine sex differences. To detect possible associations, bivariate correlation analyses with Pearson's coefficient were performed for interval-scaled variables. Canonical correlations were performed to detect possible multivariate correlations. To minimize the impact of missing data in the canonical correlation analysis, mean imputation was used. For all statistical tests, a p-value of <0.05 was set as the limit for statistical significance. Questionnaires that were incompletely answered or had missing values were excluded from further analysis.

Results

Basic clinical data

All patients displayed elevated 24 hour mean blood pressure (BP) values for both systolic and diastolic BP (mean: 148 ± 96 mmHg). In comparison to female participants, males displayed significantly higher BP. The BMI was numerically higher, the waist-to-hip ratio was significantly higher in males ($p=0.001$). No statistical significance between the sexes was observed in clinical laboratory data (*see Table 1*). 6 out of 10 females have been postmenopausal. Sex hormones have not been assessed. Cortisol co-secretion was assessed in 15 patients with dexamethasone-suppression-test (DST) and salivary profile. Only one female patient had an elevated cortisol concentration in the salivary profile. Serum cortisol was within the normal ranges for all patients.

Neuropsychological assessment

Raw scores of male and female patients did not differ significantly in any of the neuropsychological parameters (*see Table 1*). In comparison with a norm sample, patients' performance was average for most of the measures. Isolated impairments ($PR \leq 16$) could be observed in memory and attention measures, whereas half of the subjects showed impairment in at least one cognitive parameter. None of the values were far below average ($PR < 2$) (*see Figure 1*).

Psychiatric scales

On average, female PA patients scored higher in all psychiatric scales in comparison with male PA patients. Concerning the HAM-D score, difference reached statistical significance in favor of the female participants ($p = 0.025$) (*see Table 1*).

Referring to the depression-related scales, PA participants showed a mild depression severity in the PHQ-9.

Regarding the BDI and the HAM-D, the PA group stayed below the cut-off for a considerable depression severity. But when analysed separately for gender, females showed higher scores than males.

In terms of anxiety-related scales, the PA group achieved higher GAD-7 means in comparison to the German reference data ³⁶. Female participants showed a mild anxiety disorder, male ones stayed below the cutoff.

Evaluating the HAM-A study group score, our group stayed below the cut-off set by Hamilton et al. ³⁷.

SF-12

In both the physical (PCS) and the mental (MCS) SF-12 subscale, female PA participants in comparison to male PA participants showed lower mean values without reaching statistical significance. Referring to the German reference data (SF-12 Manual), the PA group explored in the present study showed lower mean values in both subscales.

Sleep questionnaires - ESS and PSQI

ESS

Male PA patients scored higher in comparison to female PA patients without reaching statistical significance ($p = 0.427$). Compared to the population-based study by Sauter et al. ⁴¹, higher scores were found in the PA group in the whole group. (see table 1)

PSQI

Female PA participants achieved higher scores in the global PSQI score as well as in all PSQI

subscales, except the "Daily Disturbances Sum Score", the "Sleep Duration Component Score", and the "Daytime Dysfunction Component Score" without reaching statistical significance (see Table 1 for p-values). Referred to the normative study by Zeithofer et al. ³⁹, the PA group showed higher mean values in the global PSQI score as well as in all PSQI subscale scores except for the "Use of sleeping medication subscale" score. (see Table1)

Significant Correlations

Significant correlations including the neuropsychological variables are listed in *Table 2*. On a multivariate level, no significant correlations appeared. Observing bivariate associations, the total number of items processed ("GZ") showed negative associations with depression- as well as anxiety-related scales. These negative associations were partly present in the male PA subgroup without equivalent in the female PA subgroup. Additionally, the percentage of errors ("F%") correlated negatively with the Physical Health Composite Scale score (PCS) of the SF-12 in the male PA group.

Both male and female PA participants showed a negative correlation between the PSQI and neuropsychological parameters, the negative association including the ESS was limited to the male PA group.

Observing hormonal associations, neuropsychological parameters correlated negatively with the plasma renin concentration in the male PA group and positively with serum aldosterone levels in the female PA group.

4. Discussion

The aim of our study was to shed light on the effects of aldosterone and MR on attention and memory functions in patients with PA treated with standardised medication. Although patients with a manifest psychiatric disorder according to DSM-IV were excluded, anxiety and depressive symptoms were elevated and QoL was reduced with higher affection in female patients as described in previous studies ^{1,2}. Sleep quality measured by PSQI was subjectively impaired in PA. All patients scored within the norm values of the general population in all tested cognitive dimensions (attention, logical memory,

executive functions). No significant differences between male and female patients were detected. However, half of the participants showed at least impairment in memory and attention measures.

Overall, a significant negative correlation for quantitative performance, measured with GZ and depression and anxiety was found, gender-specific analyses revealed that this effect was only significant in males. In males experienced anxiety and depression as well as sleep disturbances and daytime sleepiness are significantly negative correlated with quantitative performance, meaning a deceleration in their processing speed. Qualitative performance was negatively correlated with physical subscale in males. The cognitive profile of male patients was otherwise neither comparable to patients with anxiety disorders, for whom impairments in attention, memory and emotional intelligence have been described (Chutko LS et al. 2014, Castaneda AE et al 2007), nor patients with depression, for whom impairments in attention, executive functions and memory have been reported ⁴⁵. In females, GZ was positively correlated to aldosterone. Although the number of subjects is small, this finding is not in line with the assumption of aldosterone being a risk factor for cognitive impairment ^{20, 21}. Only in females subjective sleep quality in the PSQI had a negative influence on executive functions measure by abstract reasoning.

The absence of specific patterns in cognitive impairment could be explained by the fact, that patients did not reach DSM-IV or ICD-10 criteria to be diagnosed with a depression or anxiety disorder, but only showed elevated levels of symptoms compared with the general population.

Neuropsychological dimensions were not systematically associated with any of the physical parameters such as blood pressure or aldosterone. There are hints that aldosterone is associated with lower cerebrovascular function in hypertension ^{20, 21} and the association between early stage Alzheimer's disease and plasma renin-angiotensin-system aminopeptidase activities could be gender specific ⁴⁶. We found significant correlations between aldosterone and GZ in females and plasma renin and DST in males, but further investigation is warranted. Differences to other studies might be explained by the younger age of our patients in contrast to patients of the other studies.

Several studies investigated the role of the MR, the main target of aldosterone, in memory processes. These studies suggest MR to be mainly involved in fear memory and emotional arousal as well as the processing of this information ⁴⁷. In our sample of patients with PA, chronic exposure to high concentrations of aldosterone did not show marked effects on cognition. This is in contrast to previous

finding in healthy male subjects, where acute blocking of the MR with spironolactone resulted in consecutive impairment in several cognitive dimensions ¹⁵. These contrasting findings could be due to different underlying mechanisms associated with chronic exposure to aldosterone versus acute blockade with a MR antagonist. Sex differences in memory functions related to MR function have been described in animal data ⁴⁸ and sexually dimorphic regulation of the MR and gender specific effects of aldosterone are at least described for other tissues ^{49, 50}.

Chronic aldosterone excess seems not to influence immediate and delayed memory, cognitive and quantitative performance, abstract reasoning and the processing speed in our younger sample systematically. Emotional memory processes should be issue of further investigations. Sexually dimorphic regulation processes in effects of aldosterone and MR mediated processes are indicated by these data, because aldosterone was significantly associated with quantitative performance in women.

This study is limited by a small number of patients. Due to the small group of female patients, no analytical discrimination in pre- and post-menopausal status was done. A comparison with hypertensive patients would be interesting in future studies. Strengths of this study is an investigation under standardized conditions and a very good characterisation that enabled to assess possible interfering factors like fatigue or sleeping disturbances.

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Disclosure:

The authors report no conflicts of interest in this work. Beuschlein Felix is on the editorial board of EJE. Beuschlein Felix was not involved in the review or editorial process for this paper, on which he/she is listed as an author.

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Figure 1. Neuropsychological assessment

Indication of individual data for males and females according to their neuropsychological performance

Tables

Table 1. Clinical data of the patients studied

	Whole Group	PA Men	PA Women	p-value
Number N	19	9	10	-
Age (in y)	47.1 (12.5)	48.4 (10.9)	45.9 (14.3)	-
Mean time until first diagnose (months)	112.8 (101.8)	113.3 (65.3)	112.5 (130.3)	-
Mean 24h systolic BP in mmHg	148 (15)	154 (18)	143 (8)	0.124
Mean 24h diastolic BP in mmHg	96 (9)	100 (8)	91 (8)	0.023
Mean systolic BP at daytime in mmHg	150 (16)	155 (20)	145 (11)	0.217
Mean diastolic BP at daytime in mmHg	97 (10)	101 (10)	92 (8)	0.114
Mean systolic BP at night in mmHg	141 (14)	150 (13)	131 (6)	0.002
Mean diastolic BP at night in mmHg	89 (10)	96 (5)	81 (9)	<0.001
Waist-To-Hip Ratio	0.9 (0.1)	0.9 (0.1)	0.8 (0.1)	0.001
Body mass index in kg/m ²	27.2 (3.9)	28.8 (3.6)	25.7 (3.8)	0.104
Serum sodium in mmol/l (<i>135 – 150 mmol/l</i>)	141 (3)	141 (3)	140 (3)	0.765
Serum potassium (<i>3.5 – 5.0 mmol/l</i>)	3.5 (0.5)	3.4 (0.4)	3.6 (0.6)	0.317
Serum cortisol (<i>1.8 bis 24.0 µg/dl</i>)	13 (4)	14 (4)	12 (4)	0.508
Serum aldosterone (<i>40 – 310 ng/l</i>)	231 (184)	200 (138)	258 (222)	0.534
Plasma renin concentration (<i>8 – 99 µU/ml</i>)	4.4 (3.8)	4.6 (4.9)	4.1 (2.5)	0.702
Aldosterone / renin ratio (<i><20 ng/l/mU/l</i>)	79.8 (75.9)	84.2 (95.9)	75.8 (57.5)	0.889
GZ (raw data)	404 (48)	420 (42)	389 (51)	0.222
GZ	29.6 (18.2)	35.4 (19.5)	23.9 (16.0)	
GZ-F (raw data)	390 (46)	404 (43)	377 (49)	0.277
GZ-F	33.4 (19.8)	38.5 (23.1)	28.4 (15.9)	
F% (raw data)	3.8 (2.9)	4.5 (2.2)	3.0 (3.4)	0.276
F%	64.6 (23.6)	56.8 (18.2)	72.5 (26.8)	
Logical Memory I (raw data)	27.9 (6.3)	28.4 (5.7)	27.5 (7.2)	0.813
Logical Memory I	52.7 (32.2)	57.3 (28.4)	48.1 (36.9)	
Logical Memory II (raw data)	25.1 (6.2)	25.3 (6.0)	24.9 (6.8)	0.926
Logical Memory II	52.3 (30.3)	54.8 (24.9)	49.8 (36.6)	
Matrices (WIE) (raw data)	17.2 (6.0)	18.8 (6.2)	15.6 (5.7)	0.190
Matrices (WIE)	59.5 (28.7)	66.0 (28.4)	53.0 (29.4)	
DST (WIE) (raw data)	74.1 (10.9)	74.9 (9.1)	73.3 (13.2)	0.800
DST (WIE)	62.0 (25.6)	60.4 (28.4)	63.6 (24.2)	

PHQ-9	6.5 (5.3)	5.8 (5.8)	7.4 (4.9)	0.525
Reference value (RV) (cut-off: <5)	<i>3.56 (4.08)</i>			
HAM-D	5.8 (5.5)	3.2 (2.7)	8.4 (6.4)	0.025
RV (cut-off: ≤8)	<i>3.2 (3.2)</i>	<i>3.3 (3.3)</i>	<i>3.1 (3.2)</i>	
BDI	4.2 (6.2)	2.1 (3.4)	6.6 (7.9)	0.118
(cut-off: <10)				
GAD-7	5.6 (5.6)	3.6 (3.5)	7.9 (6.8)	0.076
RV (cut-off: <5)	<i>2.95 (3.41)</i>	<i>2.66 (3.24)</i>	<i>3.20 (3.52)</i>	
HAM-A	7.4 (7.1)	4.8 (4.9)	10.1 (8.1)	0.153
RV (cut-off: <14)				
SF-12; PCS	45.3 (12.1)	46.8 (11.7)	43.0 (13.4)	0.416
RV		<i>50.2 (8.68)</i>	<i>47.9 (9.74)</i>	
SF-12; MCS	50.8 (9.1)	51.0 (7.5)	50.6 (11.9)	0.936
RV		<i>53.25 (7.57)</i>	<i>51.30 (8.41)</i>	
ESS	8.1 (4.7)	8.8 (4.6)	7.4 (4.9)	0.427
RV	<i>6.6 (3.5)</i>	<i>6.9 (3.3)</i>	<i>6.2 (3.7)</i>	
PSQI- Global Score	6.4 (4.1)	6.1 (4.7)	6.7 (3.8)	0.675
RV	<i>4.55 (3.71)</i>	-	-	
PSQI- Subjective Sleep Quality	1.4 (0.7)	1.3 (0.7)	1.6 (0.8)	0.462
RV	<i>0.75 (0.78)</i>			
PSQI- Sleep Latency	1.3 (1.0)	1.00 (1.0)	1.6 (0.9)	0.141
RV	<i>0.88 (0.85)</i>			
PSQI- Sleep Duration	0.9 (0.9)	1.00 (1.0)	0.9 (1.1)	0.907
RV	<i>0.74 (0.71)</i>			
PSQI- Habitual Sleep Efficiency	0.5 (0.9)	0.3 (1.0)	0.7 (0.8)	0.411
RV	<i>0.31 (0.71)</i>			
PSQI- Sleep Disturbances	1.3 (0.7)	1.2 (0.7)	1.3 (0.8)	0.714
RV	<i>0.83 (0.99)</i>			
PSQI- Use of Sleeping Medication	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-
RV	<i>0.23 (0.68)</i>			
PSQI- Daytime Dysfunction	1.0 (0.9)	1.2 (1.2)	0.7 (0.5)	0.359
RV	<i>0.82 (0.76)</i>			
PSQI- Sleep Efficiency Sum Score	1.4 (1.7)	1.3 (1.9)	1.6 (1.6)	0.719
PSQI- Perceived Sleep Quality Sum Score	2.7 (1.5)	2.3 (1.5)	3.1 (1.6)	0.194
PSQI- Daily Disturbances Sum Score	2.3 (1.5)	2.4 (1.5)	2.0 (1.2)	0.668

Table 2. Significant Correlations

Group	Parameters			Correlation Coefficient	Sig.
Whole Group	Neuropsychological assessment - Psychiatric, Quality of life and Sleep scales	GZ	PHQ-9	-0.552	0.033
		GZ	GAD-7	-0.679	0.005
		GZ	HAM-A	-0.572	0.021
		GZ	HAM-D	-0.528	0.036
PA Men	Neuropsychological assessment - Psychiatric, Quality of life and Sleep scales	GZ	PHQ-9	-0.799	0.017
		GZ	GAD-7	-0.840	0.009
		GZ	ESS	-0.728	0.040
		GZ	PSQI	-0.774	0.024
		F%	SF-12 (PCS)	-0.732	0.039
	Neuropsychological assessment - Hormones	DST (WIE)	Plasma renin	-0.878	0.004
PA Women	Neuropsychological assessment - Psychiatric, Quality of life and Sleep scales	Matrices (WIE)	PSQI	-0.918	0.010
	Neuropsychological assessment - Hormones	GZ	Serum aldosterone	+0.729	0.040

Figures

Figure 1. Neuropsychological assessment

Indication of individual data for males and females according to their neuropsychological performance

